REMARKS/ARGUMENTS

35 U.S.C. §112, First Paragraph

Claims 1-8, 12-13, and 16-17 are rejected under 35 U.S.C. § 112 first paragraph. The Examiner states that although the specification is enabling for a cotton seed oil modified liquid carrier, it is allegedly not enabling for other modified liquid carriers. Applicants respectfully disagree. The terms "modified" and "modification" are defined as referring to "an unsaturated vehicle which, through physical, chemical or mechanical means, has been altered as compared to its natural (or "un-modified" in the case of synthetic liquid carriers) form such that the modified vehicle has an increased level of oxidation products (page 8). The types of unsaturated oils which may be modified are described beginning on page 6 of the specification. Those skilled in the art are aware that unsaturated oils are subject to oxidation to produce hydroperoxides. The level of peroxides may be expressed as the peroxide value. (See Fox et al., Tribology International, 40:1035-1046, 2007, specifically pages 1037-1038, and Adhvaryu et al., Thermochimica Acta, 364:87-97, 2000, specifically pages 87-88) These articles make it clear that the oxidation of unsaturated oils relates to the presence of double bonds in the molecule and is a general characteristic of unsaturated oils. Thus, the person skilled in the art would understand that cotton seed oil, as well as the other unsaturated oils set forth in the specification could readily be modified by the method disclosed in the specification. Applicants' invention does not relate to the modification of unsaturated oil, but rather relates to pharmaceutical compositions having a modified oil as a portion of the carrier. Accordingly, the person skilled in the art would understand that any of the unsaturated oils described in the specification could be modified, and used in Applicants' invention. Reconsideration and withdrawal of this rejection is respectfully requested.

35 U.S.C. §112, Second Paragraph

Claims 1-8, 12-13, and 16-17 are rejected under 35 U.S.C. § 112 second paragraph. In making this rejection the Examiner alleges that the term "modified carrier" is unclear because it is "unclear whether the modification is functional or structural and how the modification is

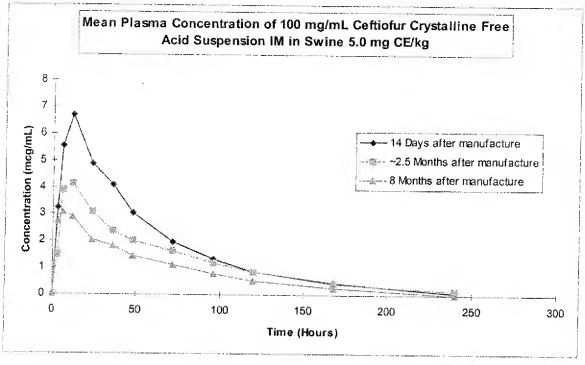
defined." Applicants respectfully disagree. The terms "modified" and "modification" are defined as referring to "an unsaturated vehicle which, through physical, chemical or mechanical means, has been altered as compared to its natural (or "un-modified" in the case of synthetic liquid carriers) form such that the modified vehicle has an increased level of oxidation products (page 8). The method of accomplishing modification and the method of measuring the peroxide levels are also defined on page 8. The types of unsaturated oils which may be modified is described beginning on page 6 of the specification. With all this information it is respectfully submitted that the person skilled in the art has no doubt about the meaning of the term "modified liquid carrier." Reconsideration and withdrawal of this rejection is respectfully requested.

35 U.S.C. §103(a) Dunn (US 5,721,359) in view of Foster (US 5,736,151)

Claims 1-8, 12-13, and 16-17 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Dunn (US 5,721,359) in view of Foster (US 5,736,151). In making this rejection the Examiner states that "Dunn teaches that the composition is sustained-release, see claim 9, column 19." The Examiner further states that "Dunn teaches modifying the oil carrier by heat or irradiation in order to render it sterile, see column 8, lines 42-50." For reasons set forth more fully below, Applicants respectfully disagree.

The compositions of Dunn (US 5,721,359) do not provide sustained release performance of the compositions of the present invention. Specifically, the compositions of Dunn do not provide predictable sustained release of one or more bioactive agents upon administration immediately after manufacture of the composition and throughout their shelf life. A formulation containing 100 mg/ml crystalline ceftiofur free acid was prepared according to example 4 of Dunn. The formulation was administered intra-muscularly to swine at 14 days, approximately 2.5 months and 8 months after preparation at a dose of 5.0 mg of ceftiofur equivalent (CE)/kg body weight. Although there were no noticeable changes in the formulation's potency, the release profile of the formulation changed noticeably over time. This is illustrated by the following graph.

In-vivo Drug Release Profile Changes Over Time for 100 mg/ml Crystalline Ceftiofur Free Acid Formulation of the Dunn Patent Administered IM in Swine



In referring to Dunn, the Examiner further states that "Dunn teaches modifying the oil carrier by heat or irradiation in order to render it sterile, see column 8, lines 42-50." Applicants respectfully disagree. The passage in question reads (column 8 lines 42 to 50):

> "Carriers and vehicles include vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols, for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like. Any solid preparations for subsequent extemporaneous preparation of sterile injectable preparations are sterilized, by exposure to heat, cobalt 60 irradiation, or by exposure to a sterilizing gas, for example, ethylene oxide."

The issue is whether the phrase "solid preparations" refers to solids in a carrier or simply solids. If the term "solid preparations" refers simply to solids, then the carrier is not present when these preparations are being irradiated or heated. Dunn discloses three methods for sterilizing the solid preparations, that is, heat, cobalt 60 irradiation, and exposure to ethylene oxide. As noted in Remington, The Science and Practice of Pharmacy (19th Edition p. 765), ethylene oxide is not

generally used to sterilize liquids. Ethylene oxide is toxic, carcinogenic, teratogenic, and difficult to remove from the objects being sterilized. Products sterilized with ethylene oxide need to be quarantined for about fourteen days to eliminate the absorbed residues of ethylene oxide. As noted in the Matheson Tri-Gas MSDS for ethylene oxide, it is soluble in water and organic solvents. Thus, if ethylene oxide were used to sterilize a solid in one of the carriers described by Dunn, it would dissolve in the carrier and would not be readily removed. Ethylene oxide residues are not desirable in a pharmaceutical product. Applicants also note that in the passage above, Dunn refers to "solid preparations for subsequent extemporaneous preparation of sterile injectable preparations..." Clearly, the term "solid preparations" does not refer to solids in a carrier because these preparations require further steps to produce "sterile injectable preparations." If a carrier were present, the preparations would be suitable for injection, and would not require further processing.

Applicants further respectfully submit that the term "solid preparations" refers to a dosage form. Dosage forms are discussed in Dunn (column 8 lines 14 to 20):

> Examples of suitable dosage unit forms in accordance with this invention are liquid preparations in suitable liquid vehicles for intramuscular, intramammary and intravenous administration, suppositories and sterile dry preparations for the extemporaneous preparation (mixing just prior to administration) of sterile injectable preparations in a suitable liquid vehicle or for administration as a solid implant.

Applicants respectfully submit that the person skilled in the art would conclude that in the passage in Dunn, quoted above, the term "solid preparations for subsequent extemporaneous preparation of sterile injectable preparations" (column 8 lines 47 to 48) refers to the dosage form described as "sterile dry preparations for subsequent extemporaneous preparation (mixing just prior to administration) of sterile injectable preparations" (Column 8 lines 17 to 19). Clearly this dosage form is a dry solid, and Applicants respectfully submit that the "solid preparations" (column 8 line 47) are dry solids. Since the carrier is not present when the solid preparations are being sterilized, the carrier is not subject to heat or irradiation. Thus, Dunn does not teach the modified vehicles used in Applicants' invention.

Foster teaches a formulation containing ceftiofur HCl in an oil carrier that includes a

small amount of water (column 5 lines 8 to 18). Foster does not teach a formulation comprising a modified carrier. Foster also recommends dosing once a day (column 8 lines 16 to 18), and thus provides an immediate release formulation, not a sustained release formulation. Neither Dunn nor Foster provide for a modified carrier. Neither the compositions of Dunn or Foster provide predictable sustained release of one or more bioactive agents upon administration immediately after manufacture of the composition and throughout their shelf life. Taken separately or together, the two references do not provide a teaching of Applicants' invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Applicants respectfully request reconsideration and withdrawal of all rejections. Allowance of the present application is earnestly requested.

The commissioner is hereby authorized to debit Deposit Account No. 16-1445 for any underpayments overseen by Applicants in relation to this response.

If the Examiner believes that personal communications will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this application is respectfully requested.

Respectfully submitted,

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Enclosures